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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,969	05/08/2001	Randolph J. Noelle	037003-0280613	1327

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/849,969	NOELLE, RANDOLPH J.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-10,12-14,17 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-10,12-14,17 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 11/6/06, has been entered.
Claims 1 and 12 have been amended.

Claims 1, 5-10, 12-14, 17 and 19 are pending and being acted upon presently.

Claims 2-4, 11, 15-16, 18 and 20-21 have been canceled previously.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments in the amendment, filed 11/6/06.
The rejections of record can be found in the previous Office Action, mailed 5/4/06.

3. Upon reconsideration of applicant's amended claims, filed 11/6/06, the previous rejection under 35 U.S.C. 112, second paragraph, with respect to the recitation of "T cell mediated autoimmune responses associated with type I diabetes" has been withdrawn.

4. Claims 1, 5-10, 17, and 19 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed:
"wherein the anti-gp39 antibody or fragment binds to an epitope recognized bound by a monoclonal antibody produced by the 24-31 hybridoma" essentially for the reasons of record.

Applicant's arguments, filed 11/6/06, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's amendment, filed 11/6/06, relies upon amending the claims to recite "wherein the anti-gp39 antibody fragments binds to an epitope recognized by a monoclonal antibody produced by 24-31 hybridoma, ATCC Acession Number HB 11712" and the disclosure as-filed with respect to methods of making anti-gp39 antibodies and to the preferred anti-human gp39 antibodies 24-31 and 89-76 to support the written description and possession of the claimed methods.

Again, it appears that applicant acknowledges that the particular "limitation" does not have written description in the specification as filed; therefore the claims represent a departure from the specification and claims as originally filed.

Once again, applicant's reliance on generic disclosure of anti-gp39 antibodies (see pages 4-6 of the specification) and a single species of anti-gp39 antibodies produced by the 24-31 hybridoma (see page 6, paragraph 2 of the instant specification) do/does not provide sufficient direction and guidance to the features of establishing a new subgenus "a 24-31 antibody epitopic specificity", as currently claimed

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Obviousness is not the standard for the addition new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Applicant also relies upon the referenced teachings of WO 95/06666, which issued to U.S. patent No. 5,747,037 for teachings methods of making anti-gp39 antibodies as well as describing the 24-31 monoclonal antibody.

Applicant is reminded that to incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where the material is found in the various documents. See Advanced Display Systems, Inc. v. Kent State Univ., 54 USPQ2d 1673 (Fed. Cir. 2000) citing In re Seversky, 177 USPQ 144, 146 (CCPA 1973).

Here, applicant has not pointed out with sufficient specificity and particularity as to the written support for the recitation of the claimed epitopic specificity, that is, "wherein the anti-gp39 antibody or fragment binds to an epitope recognized bound by a monoclonal antibody produced by the 24-31 hybridoma" in the instant host document as-filed, including reliance upon a nexus to WO 95/06666 (e.g., see page 6, paragraph 2 of the instant specification).

A showing of possession of generic methods to make anti-gp39 antibodies and the provision of a specific species of anti-gp39 antibodies, namely 24-31, is ancillary to the statutory mandate that "[t]he specification shall contain a written description of the invention," and that requirement is not met if, despite a showing of possession, the specification does not adequately describe the claimed invention.

However, such a showing of possession of generic methods to make anti-gp39 antibodies and the provision of a specific species of anti-gp39 antibodies does not cure the lack of a written description in the specification, as required by statute, to provide adequately describe the claimed epitopic specificity in the specification as-filed.

The specification as filed does not provide a sufficient written description of specific "limitations" within this newly submitted phrase. The specification does not provide sufficient blaze marks nor direction for the instant methods encompassing the above-mentioned "limitations" as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP 714.02 and 2163.06

Applicant's arguments have not been found persuasive.

5. Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Applicant's arguments, filed 11/6/06, have been fully considered but have not been found convincing for the reasons of record, reiterated herein for applicant's convenience.

While applicant submits that it would have been readily understood by the ordinary artisan at the time the invention was made that that antibodies or fusion proteins (?) containing CDRs which bind to the epitope bound by antibody 24-31 may also contain a hypervariable region of monoclonal antibody 24-31 as well as the known use of antigen-binding portions such as hypervariable regions (CDRs) to make antibodies to antigens of interest,

applicant is reminded that the claims recite "a hypervariable region of monoclonal antibody 24-31".

Applicant's assertions about CDRs and antigen-binding regions are consistent with the rejection of record.

However, the claims do not necessarily provide for a functional antibody in the absence of all of the critical hypervariable region (e.g., six (6) CDRs) of an antibody, but rather, rely upon a single CDR from antibody 24-31.

Again, the following is reiterated for applicant's convenience.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

For example, even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 79: 1979- 1983,1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an gp39-/CD40L-specific antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding and inhibitory functions to prevent T cell mediated immune responses / tissue destruction.

The specification provides insufficient direction or guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional humanize antibody can be obtained by replacing the CDR regions of an acceptor antibody with the CDRs of a donor antibody. As evidenced by Adair et al. (US Patent 6,632,927) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (see column 2, lines 58-61).

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention

Applicant's arguments have not been found persuasive for the reasons of record.

Again, applicant is invited to amend the claims to provide for a functional gp39-specific / CD40L-specific antibodies that can prevent T cell mediated immune responses / tissue destruction, encompassed by the claimed methods.

6. As indicated previously for examination purposes, the claims can be read on preventing the elaboration of T cell mediated tissue destruction / autoimmune responses associated with type I diabetes as part of a therapeutic regimen during the treatment of type I diabetes rather than being limited to preventing type I diabetes per se.

7. Claims 1, 5-10, 12-14, 17 and 19 are rejected under 35 U.S.C.§ 103(a) as being unpatentable Lederman et al. (U.S. Patent No. 6,592,868) in view of Noelle et al. (U.S. Patent No. 5,747,037) for the reasons of record.

Applicant's arguments, in conjunction with the 132 Clark Declaration and Exhibits, filed 11/6/06, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments, including the reliance upon the 132 Clark Declaration and Exhibits and the examiner's rebuttal are essentially the same of record, other than the provision of the 132 Declaration and Exhibits.

Applicant argues in conjunction with the 132 Clark Declaration / Exhibits that the prior art is based upon incorrect assumptions and that methods of inhibiting T cell-mediated immune responses at the time the invention was made with gp39 antagonists lacked a reasonable expectation of success (e.g., June 1995).

Applicant also submits that the prior art, particularly Lederman et al. is limited to inhibiting humoral or B-cell mediated immune responses.

Applicant acknowledges that the prior art inhibited T cell – B cell interactions and that antigen-presenting cells are important in generating immune responses.

However, it appears that applicant does not mention that B cells are important antigen-presenting cells in humans (e.g., see Noelle et al., column 10, paragraph 1); that Noelle et al. does teach inducing T cell tolerance or non-responsiveness via gp39 antagonists; that both Lederman et al. and Noelle et al. (co-inventor) do teach treating autoimmunity as well as other conditions associated with T cell immune responses with gp39 / CD40L / 5C8 antagonists and that Lederman et al. teach and claim methods of treating diabetes (e.g., see Claim 7 of Lederman et al.).

Applicant's arguments, including the reliance upon the 132 Clark Declaration and Exhibits focus on mechanisms and not on the teachings of the prior art set forth in the rejection of record.

In contrast to applicant's assertions,
the prior art of record is not required to provide actual efficacy for the specifically claimed methods to render the instant claims obvious.

Other than relying on asserted differences in mechanisms of action based upon the asserted teachings of the prior art set forth in the rejection of record and that relied upon in the 132 Declaration and Exhibits,
applicant has not distinguished between the motivation and expectation of success in treating the same patient populations, namely patients with diabetes, with the same gp39 / CD40L / 5C8 antagonists, namely gp39- / CD40L- / 5c8- specific antibodies.

Applicant is reminded that U.S. patents are presumed valid by U.S. courts, unless proven otherwise.

While applicant and the 132 Clark Declaration are essentially indicating the treating the T cell-mediated tissue destruction associated with type I diabetes would not have been expected at the time the invention was made and that Lederman et al. does not provide any in vitro or in vivo data to support their patent,
applicant has not addressed the presumption of validity as well as the clear teachings of the Lederman et al. patent, which includes methods of treating diabetes with gp39- / CD40L- / 5C8-specific antibodies.

While Lederman et al. tests and directs the ordinary artisan to inhibiting T cell – B cell interactions with 5c8 (i.e., gp39 / CD40L) antagonists, including inhibiting humoral immune responses,
Lederman et al. is not is limited as asserted by applicant and the 132 Clark Declaration. As indicated previously, Lederman et al. do teach treating diseases and conditions associated with T cell mediated immune responses.

Even applicant and the 132 Clark Declaration note that most of the diseases listed by the prior art are primary B cell-mediated, thereby acknowledging that the prior art targeted diseases also including T cell-mediated immune responses as well.

While applicant asserts that the teachings of Noelle concerning the use of gp39 antagonists in the treatment of pancreatic allografts would not suggest treating the underlying disease of such treatment, namely diabetes
Applicant appears to ignore the teachings of co-inventor Noelle et al. in the use of gp39 antagonists in inducing T cell non-responsiveness or tolerance as well as in the treatment of autoimmunity.

Applicant's assertions of unexpected results do not overcome clear evidence of obviousness of treating patients with diabetes with anti-CD40 ligand antibodies, including the 24-31 antibody at the time the invention was made

As pointed out previously, although Lederman is silent about the prevention of a T cell mediated autoimmune response associated with type I diabetes, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

"{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable. "In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See MPEP 2145.

As noted previously, although the 5c8 antibody and the instant 24-31 antibody epitope specificities nor describe "T cell mediated autoimmune responses" per se,
the prior art , including both Lederman et al. and Noelle et al. clearly provided for inhibiting cell-mediated inflammatory conditions, autoimmunity or diabetes at the time the invention was made with 5C8-specific / CD40L-specific antibodies.
The prior art teaching of Lederman et al. is not limited to treating B cell immune responses only, given its teaching of inhibiting transplant rejection and autoimmune diseases such as diabetes.

Although applicant argues that there is no suggestion in the '037 in merely administering the gp39 antagonist without antigen,
Lederman et al. does teach treating diabetes with 5c8- (gp39-, CD40 ligand-) specific antibodies in the absence of antigen presenting cells.
In addition, autoimmunity by its very nature encompasses the presence of autoantigen.
'037 provides for a more efficient method for inducing long term specific nonresponsiveness to autoantigens by providing antigen presenting cells in methods to treat an autoimmune condition such as diabetes, already taught to be treated with CD40 ligand-specific antibodies in the absence of antigen presenting cells by Lederman et al.
Further, it is noted that the claimed methods recite "comprising" which leaves the claim open for the inclusion of unspecified ingredients even in major amounts. See MPEP 2111.03.

Given the assertions of unexpected results, the prior art already provides clear direction in providing for the particular 24-31 CD40 ligand-specific antibody in the treatment of diabetes at the time the invention was made.

In this case the teachings of both the primary and second references indicate success in treating diabetic patients with anti-CD40 ligand antibodies in the face of having to solve the same or nearly the same problem would have led one of ordinary skill in the art at the time the invention was made to combine the references to treat the same or nearly the same diabetic patient populations with antagonistic therapeutic anti-CD40 ligand antibodies to dampen the well known inflammatory problems associated with diabetic patients in the art.

The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144.

In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

Given the antagonistic properties of the particular 24-31 and 89-76 CD40L-specific antibodies taught by Noelle et al. ('037), the ordinary artisan would have been motivated to substitute these CD40L antagonists into the methods of treating autoimmune diseases such as diabetes, as taught by Lederman, given their inhibitory properties were consistent with the antagonistic CD40L-specific antibodies taught by the prior art. Noelle et al. ('037) and Lederman et al. all teach the advantages of anti-CD40L antibodies to inhibit immune responses by targeting the CD40L on T helper cells in therapeutic modalities of immunosuppression at the time the invention was made. Appliant's arguments that the prior art, including Lederman et al. are only limited to treating B cell immune response only is not consistent with the a reasonable interpretation of the prior art in the applicability of CD40L-specific antibodies in the treatment of various inflammatory or immune regulated conditions and disorders, including diabetes itself.

While the prior art anti-CD40L antibodies may have been tested with respect to parameters associated with B cell activation and immunoglobulin production, the prior art clearly teaches that CD40L was expressed on important activated CD4+ T cells that regulated various immune responses and that CD40L was targeted in conditions and disorders known to be cell-mediated at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

8. No claim allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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